

# Chlorinated and Brominated Dioxins and Dibenzofurans in Human Tissue Following Exposure

by Arnold Schechter,<sup>1</sup> John J. Ryan,<sup>2</sup> Yoshito Masuda,<sup>3</sup> Paul Brandt-Rauf,<sup>4</sup> John Constable,<sup>5</sup> Hoang Dinh Cau,<sup>6</sup> Le Cao Dai,<sup>6</sup> Hoang Tri Quynh,<sup>6</sup> Nguyen Thi Ngoc Phuong,<sup>7</sup> and Pham Hoang Phiet<sup>8</sup>

With substantial improvements in analytic techniques over the past decade, it has become possible to measure polychlorinated dioxins (PCDDs) and dibenzofurans (PCDFs) in human tissue in a congener-specific fashion down to the low parts per trillion level. This paper reviews findings using these new techniques from a number of recent medical and environmental case studies. These studies include those of workers exposed to a polychlorinated biphenyl (PCB) transformer fire in the United States, German chemical workers exposed to 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) while cleaning up after an explosion, workers at a municipal incinerator in New York City, a chemist exposed to brominated and chlorinated dioxins, U.S. veterans and also Vietnamese civilians exposed to Agent Orange contaminated with TCDD in Vietnam, and victims of the polychlorinated dibenzofuran and PCB contaminated rice oil (Yusho) incident in Japan.

## Introduction

During the 1980s, markedly improved extraction and separation methods, improved capillary columns, availability of dioxin and dibenzofuran standards, and improvements in gas chromatography-mass spectrometry, greatly increased the ability of chemists to identify and quantitate chlorinated dioxins and dibenzofurans in human tissues down to the low parts per trillion level, and sometimes even lower. These technical advances permit dioxin measurements in human tissue to be used in clinical medicine and epidemiology.

Despite these rapid analytical advances and demonstrations of the usefulness of dioxin measurements in human tissue following potential exposure, the measurement of dioxins in human tissues to characterize exposure of individuals or groups is rarely used at the present time. This is partly due to the cost of analyses, between \$1,500 and \$2,500 each, the scarcity of qualified laboratories (there are between 10 and 20 worldwide), the unwillingness of health insurance carriers to pay for these analyses, and, perhaps most important, the lack of awareness among health care professionals concerning such analyses usefulness and availability.

In an attempt to show how such measurements can be of use in either clinical medicine or epidemiology, we review here selected congener-specific findings from our work this past decade, from various medical case histories. Measurement of dioxins in human tissue and food was first performed by Baughman between 1970 and 1974 (1,2). He measured 2,3,7,8-TCDD in milk collected from Vietnamese women then living in villages that had been sprayed with Agent Orange and also in food samples. Measurement of 2,3,7,8-TCDD, the dioxin characteristic of Agent Orange, in adipose tissue of U.S. Vietnam veterans was first reported in 1982 and published in 1984 (3). Elevated dioxin and dibenzofuran levels in blood and fat of American workers following exposure and measured levels in controls from the general population were first reported in the

<sup>1</sup>Department of Preventive Medicine, College of Medicine Clinical Campus, SUNY Health Science Center/Syracuse, 88 Aldrich Avenue, Binghamton, NY 13903.

<sup>2</sup>Food Directorate, Health and Welfare Canada, Tunney's Pasture, Ottawa, K109C6 Canada.

<sup>3</sup>Daiichi College of Pharmaceutical Sciences, 22-1 Tamagawa-cho Minami-ku, Fukuoka, 815 Japan.

<sup>4</sup>School of Public Health, Division of Environmental Sciences, Columbia University, 60 Haven Ave., B-2, New York, NY 10032.

<sup>5</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114.

<sup>6</sup>College of Medicine, Hanoi University, and Ministry of Health, Hanoi, Vietnam.

<sup>7</sup>College of Medicine of Ho Chi Minh City and Obstetrics and Gynecology Hospital, Ho Chi Minh City, Vietnam.

<sup>8</sup>Cho Ray Hospital, Ho Chi Minh City, Vietnam.

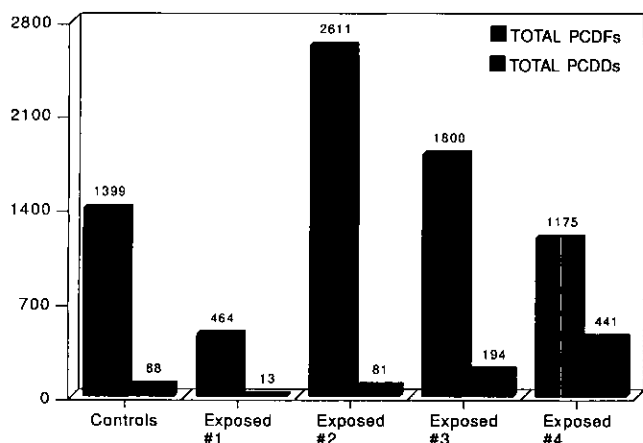


FIGURE 1. PCB transformer fire, Binghamton, New York. Total PCDD/Fs in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls=mean of eight.

United States in 1983 (4) and subsequently published (5-7). At the same time, levels of dioxins and dibenzofurans in adipose tissue from the general population were reported for Canadians (8). Later work refined the techniques used for the measurement of dioxins in American workers and controls (9).

## Methods

The analytical methods used for identifying and quantifying dioxins and dibenzofurans have been described elsewhere and are therefore only referenced here (10-14).

Human tissue was placed in chemically clean containers, usually glass bottles with Teflon-lined caps, and frozen. The tissue was stored frozen between  $-20^{\circ}\text{C}$  and  $-70^{\circ}\text{C}$  until analyzed.

## Results and Discussion

### PCB Transformer Fire in Binghamton, New York, 1981

Figure 1 presents total dioxin and dibenzofuran levels in adipose tissue from four potentially exposed workers and the mean values from matched controls obtained at a local hospital (7). All workers were potentially exposed to polychlorinated dibenzofurans and polychlorinated dibenzodioxins generated from a 1981 PCB transformer fire in Binghamton, New York (15-18). Fat biopsies and dioxin analyses were first performed 2 years after the fire. These were the first dioxin and dibenzofuran measurements reported in the United States for potentially exposed workers and also for the general population. At the time, finding dioxins and dibenzofurans in the general population controls was unexpected. Worker #1 did not have elevated dioxin or dibenzofuran levels compared to these controls. Worker #2 had elevated dioxins but not dibenzofurans, however, more dibenzofurans were produced by PCB pyrolysis from the transformer fire than were dioxins. The findings of both elevated PCDDs and PCDFs in worker #3, is consistent with intake of these compounds from the incident, the only known special exposure in his

case. Worker #4 shows elevated PCDF levels, but not elevated PCDD levels. The PCDD/F control values found in this human tissue study at about 1500 ppt were slightly higher than those in later studies, where we found mean PCDD/F levels of 1200 ppt in fat tissue.

In the absence of measurements taken before the incident or serial measurements taken over time, it was not initially obvious that elevated levels were from this incident, although the levels in some of the potentially exposed workers were clearly above control values. With the potentially exposed worker whose PCDD/F levels were below the controls, it was also not possible or reasonable to exclude the possibility of some intake of PCDD/Fs from the incident. However, it appeared reasonable to conclude that if total dioxins, total dibenzofurans, and also individual congeners were elevated and corresponded to the congeners found in environmental samples at the site, then the elevated levels probably resulted from this specific incident of exposure. From a health perspective, conversion of the dioxins and dibenzofurans from measured values to their 2,3,7,8-TCDD toxic dioxin equivalents (TEQ), comparing their toxicity with TCDD is sometimes useful (19-21). This conversion is used for the controls and the four workers in Figure 2. This shows that for the age, sex, and geographically similar hospital controls, the average total TEQ is 50 ppt with 35 ppt from dioxins and 15 ppt from dibenzofurans. We later found 20-40 ppt TEQ to be the usual levels for North American adults. For worker 1, the total is 32, for workers 2, 3, and 4, the values are 110, 92, and 109 ppt, respectively. If these values should prove to be above a threshold for toxic response, then there would be not only documentation of exposure and intake, but also cause for concern about the health of these workers.

In Figures 3-6, individual lipid-adjusted congener levels of adipose tissue are compared for these workers and controls to provide more detailed comparisons. The pyrolysis of PCBs and polychlorinated benzenes in the transformer oil produced a mixture of PCDDs and PCDFs, especially of the higher chlorinated congeners (15-18). PCDFs were generally present in the soot in greater amounts than were PCDDs. In Figure 3, 2,3,7,8-TCDD, quantitatively a minor component in some of the soot samples tested after the fire, is found to be somewhat elevated in all four

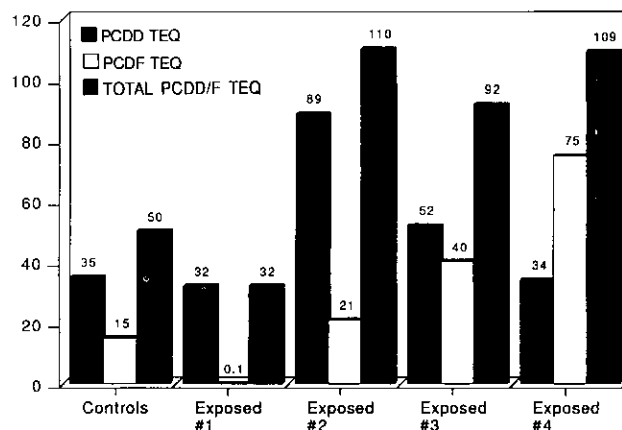


FIGURE 2. PCB transformer fire, Binghamton, New York. TEQ in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls = mean of eight.

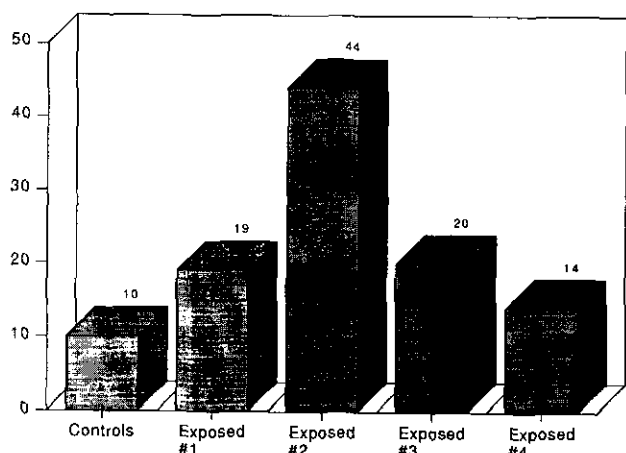


FIGURE 3. PCB transformer fire, Binghamton, New York. 2,3,7,8-TCDD in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls = mean of eight.

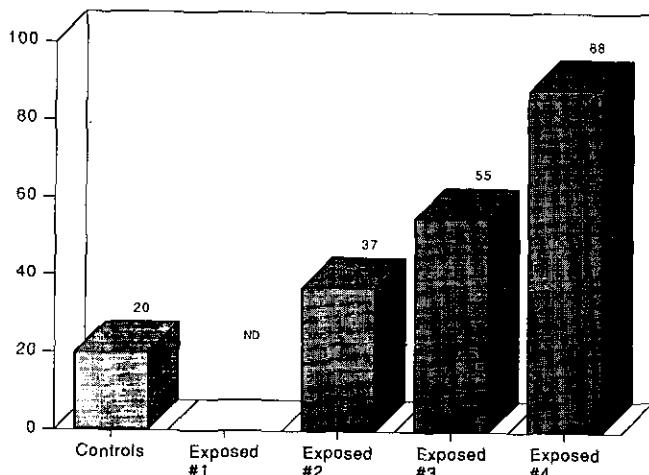


FIGURE 4. PCB transformer fire, Binghamton, New York. 2,3,4,7,8-PeCDF in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls = mean of eight.

workers when compared to the controls. It should be noted that half-life for elimination of 2,3,7,8-TCDD is believed to be longer than for the dibenzofurans. Figure 4 presents the workers' level of 2,3,4,7,8-penta(Pe)CDF. Worker 1 is below the control level, whereas the remaining three workers have elevated levels. Figure 5 shows elevation above background for workers 3 and 4 of 1,2,3,4,7,8 and 1,2,3,6,7,8-hexa(Hx)CDF. Figure 6, showing levels of 1,2,3,4,6,7,8-hepta(Hp)CDF, documents only worker 4, who had elevated levels for this congener, which was also present in some soot samples. Exposure to various congeners, intake, and elimination may be expected to vary, but the congener patterns as well as total PCDD and also PCDF values seem to be consistent with some PCDD/F intake for most in this group of workers. These levels are not as high as those later reported from other dioxin tissue analyses in different incidents (22-24).

A different approach was used for another worker who was involved in the cleanup and who exhibited the highest dioxin and dibenzofuran adipose tissue levels of those in the Binghamton

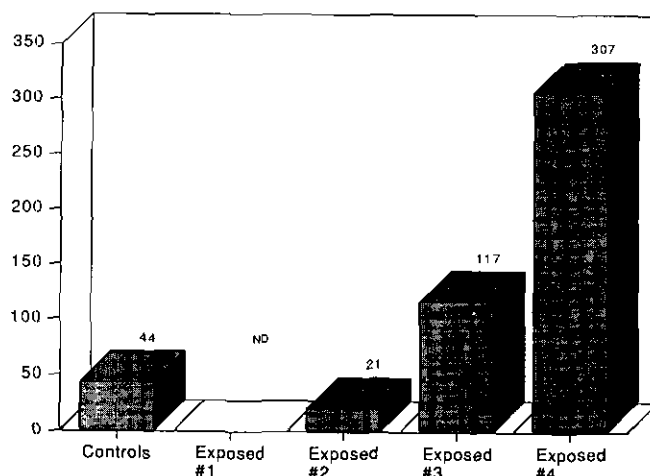


FIGURE 5. PCB transformer fire, Binghamton, New York. 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDF in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls = mean of eight.

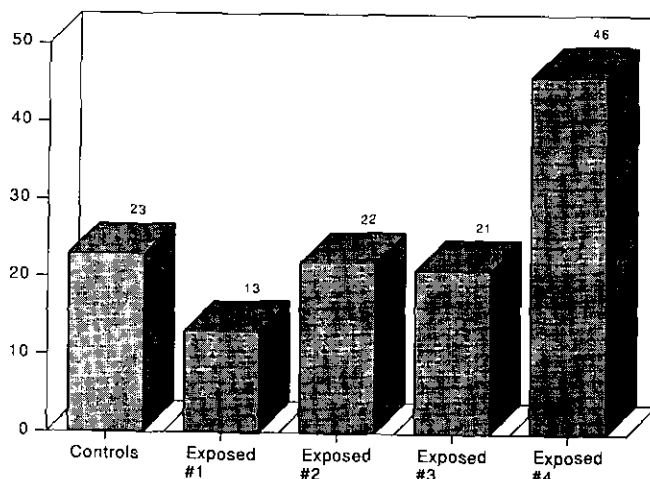


FIGURE 6. PCB transformer fire, Binghamton, New York. 1,2,3,4,6,7,8-HpCDF in adipose tissue (ppt, lipid) from workers 2 years after incident. Controls = mean of eight.

incident (12,25). For a variety of reasons, including an attempt to determine whether these chemicals were from the work-site exposure, serial fat and later blood samples were obtained for PCDD/F analyses. Figure 7 presents 2,3,4,7,8-PeCDF results from 10 samples collected over 7-year period, which began 2 years after this worker's 6-month exposure in 1981. In Figure 8, results for 1,2,3,4,7,8 and 1,2,3,6,7,8-HxCDF are presented, and the same general pattern of a steady decline over time is noted. This decline over time is consistent with the exposure in 1981. Slight increases in the 1990 levels are believed to be due to analytic variability but other explanations may exist. It is, of course, quite rare for a patient to volunteer for repeated fat biopsies or donation of 100 to 450 mL of blood for dioxin analyses. As techniques improve, smaller blood specimens may be used, and the possibility of serial blood sampling for dioxin measurement should become less difficult for all involved. The serial determinations done here are consistent with and

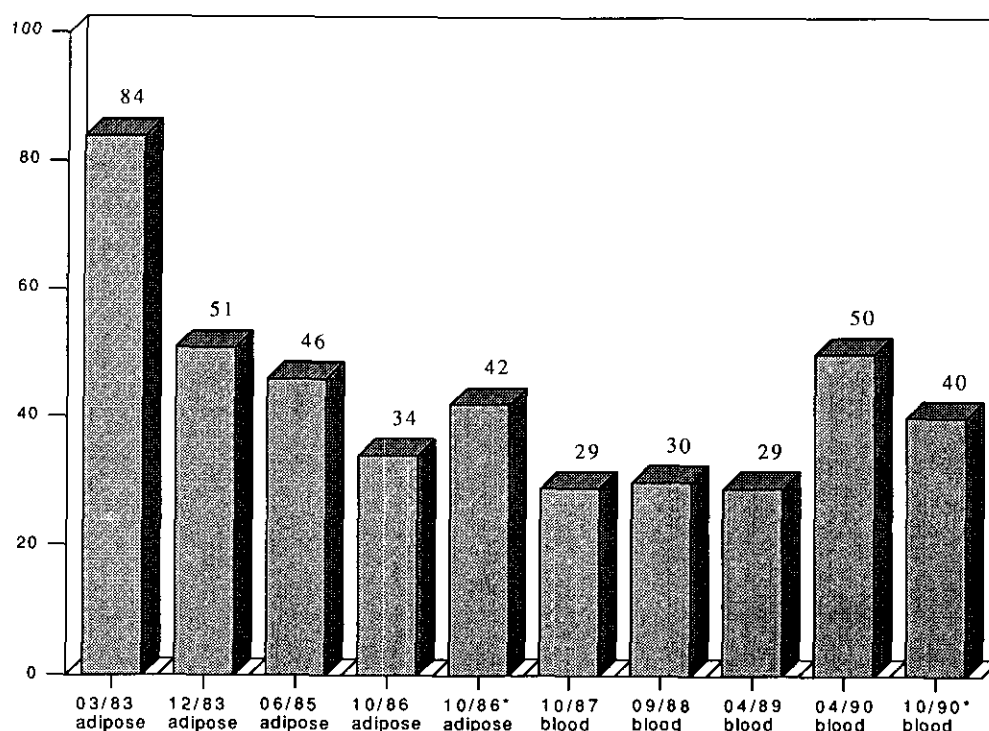


FIGURE 7. PCB transformer fire, Binghamton, New York. 2,3,4,7,8-PeCDF in serial samples (ppt, lipid) from a cleanup worker. (\*) Analyzed in 1991.

similar to studies of Yusho patients and others exposed to dibenzofurans where all findings suggest shorter half-lives of elimination for certain of the dibenzofurans than the 5–10 year value, currently believed to represent an approximate half-life for TCDD in humans (26–28). Half-lives of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8/1,2,3,6,7,8-HxCDF in this cleanup worker can be calculated to be 3.17 and 2.94 years, respectively. Our findings with this patient are consistent with the earlier findings of Gorski (29) and recent findings of Ryan and Masuda (30).

### TCDD Exposure of Workers at the BASF Factory in Ludwigshaven, Germany, 1953

Figure 9 presents adipose tissue levels of TCDD in six German workers 32 years after they worked as cleanup workers in the TCDD-contaminated BASF factory in Ludwigshaven, Germany (31). When exposure is high, dioxins can be found in human tissues at elevated levels for decades after exposure. These workers developed chloracne and other more serious illnesses during and after the cleanup. The workers wanted to have evidence for a type of workers' compensation insurance hearing to document intake of dioxins and its possible relationship to subsequent illnesses, which led to their request for fat tissue dioxin analysis. The adipose tissue TCDD levels in 1985 varied from 11 to 141 ppt lipid. We estimate levels in 1953, the time of exposure, to have been between 917 and 11,750 ppt. The mean level for German controls is about 4 ppt. The estimated body burden for TCDD for these workers, shown in Figure 10, varied from 9.7 to 124  $\mu$ g. Their estimated dose, in nanograms per kilogram of body weight, varied from 140 to 1800. For these calculations we

assumed first-order kinetics, a 5 year half-life, a single-compartment model, and also assumed that most TCDD is found in fat tissue. These levels were sufficient to cause chloracne and apparently other illnesses in each of these workers.

### Municipal Incinerator Workers, New York City, USA, 1990

Municipal incinerators characteristically produce a mixture of congeners, including tetra through octachlorinated dioxins and dibenzofurans, by burning organic compounds in the presence of chlorine. Because of concerns about bioavailability of dioxins and dibenzofurans from incinerator ash where elevated PCDD/Fs were found in meat and milk from cattle grazing near incinerators in Holland (32), incinerator workers' blood was examined (33). Pooled blood of workers from a relatively old incinerator in New York City was measured for PCDD/Fs, and the percentage increase, by congeners, was compared to a matched New York City control group of pooled blood (Fig. 11). A consistent pattern of PCDD/F congener elevation was found, with the exception of TCDD. This is similar to the findings in both meat and milk from Dutch cattle grazing near a municipal incinerator. The levels found document bioavailability and suggests that there is a hazard to workers from this currently popular method of household garbage disposal. To a lesser extent, it suggests a hazard to those living near incinerators or the dump sites for their ash. Better and more modern incinerators, and those which do not burn chlorinated products, may sometimes produce less PCDD/Fs. Personal protective measures were used for these municipal incinerator workers after these findings.

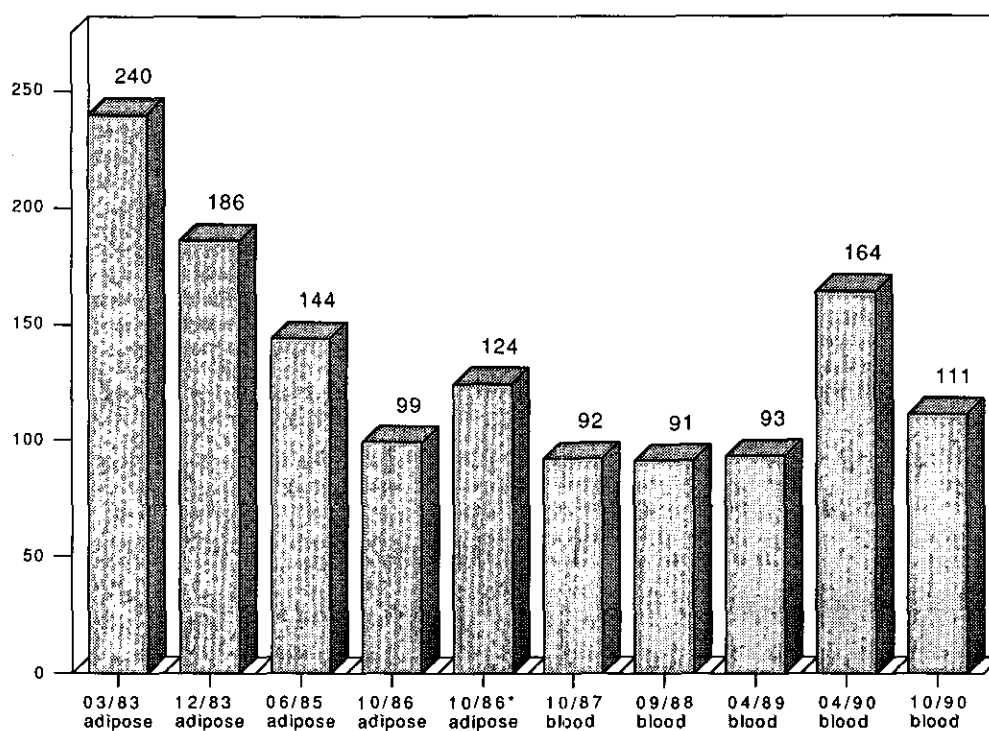


FIGURE 8. PCB transformer fire, Binghamton, New York. 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDF in serial samples (ppt, lipid) from a cleanup worker. (\*) Analyzed in 1991.

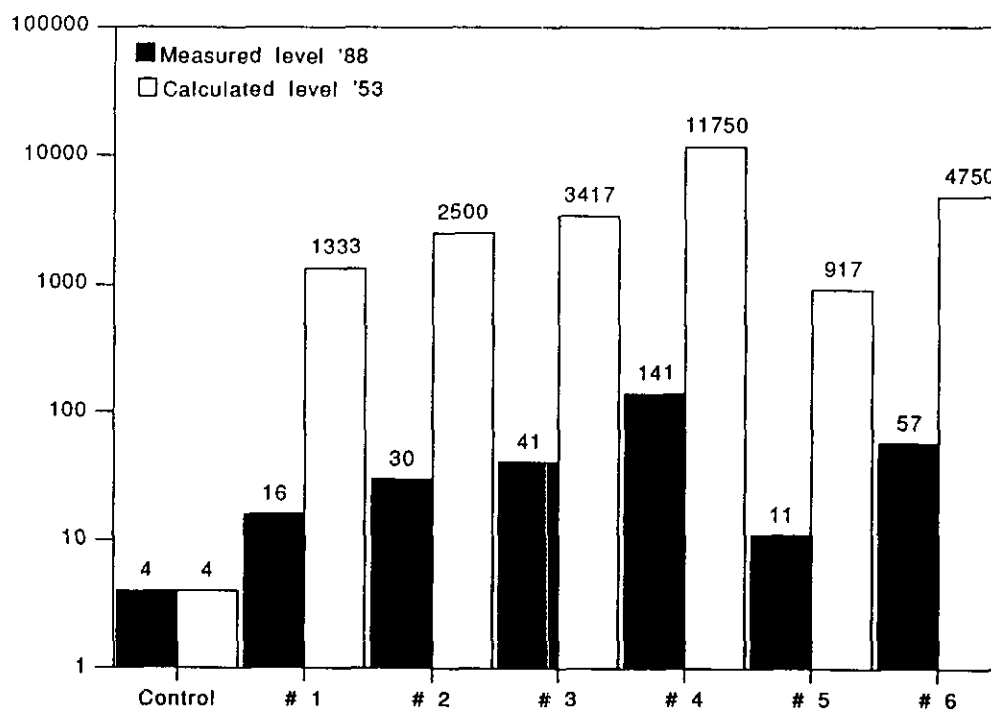


FIGURE 9. BASF factory, Ludwigshaven, Germany. 2,3,7,8-TCDD in adipose tissue (ppt, lipid) of exposed workers. Levels measured 32 years after exposure, calculated for time of exposure, 5-year half-life assumed.

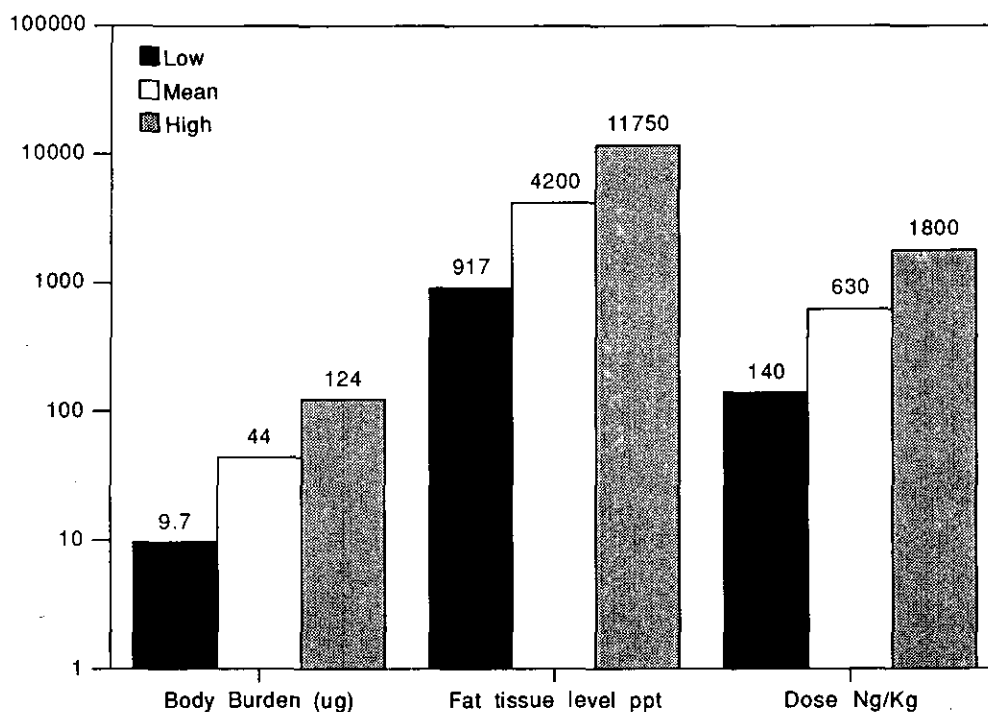


FIGURE 10. BASF factory, Ludwigshaven, Germany. Estimated body burden, tissue level (ppt, lipid), and dose of 2,3,7,8-TCDD at time of exposure. Calculated for time of exposure, 5-year half-life assumed.

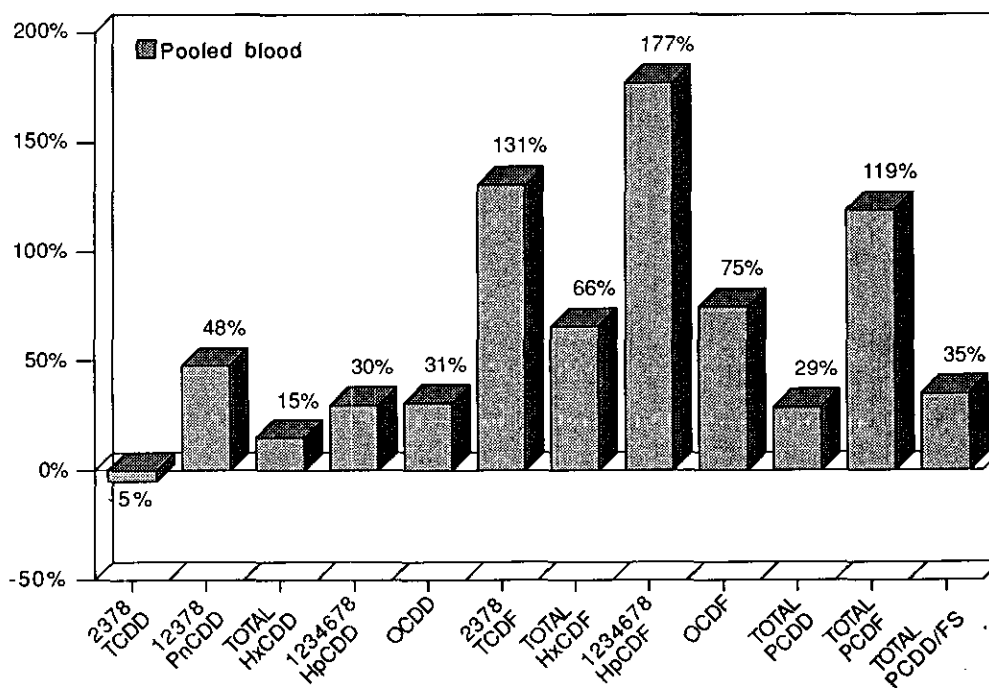


FIGURE 11. Municipal incinerator workers, New York City: percentage of increase over matched controls by congener. Workers,  $N=85$ ; controls,  $N=14$ .

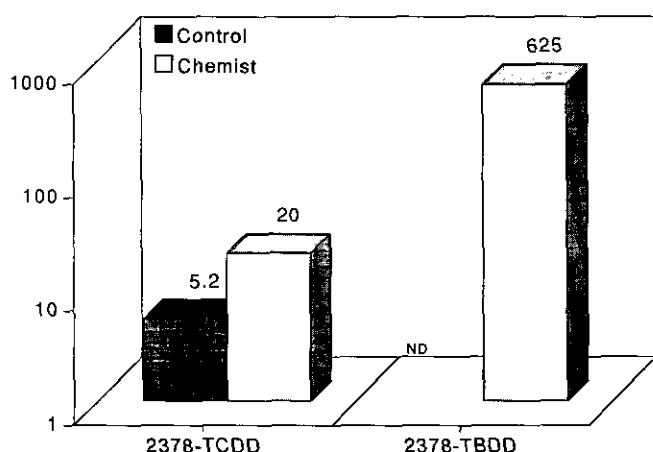


FIGURE 12. Accidental exposure to 2,3,7,8-TCDD and 2,3,7,8-TBrDD measured in blood 34 years after exposure. Control for TCDD is a pool of  $n=100$ . Control for TBrDD is mean of four analyses with detection limit of 3 ppt (lipid).

### Chemist Accidentally Exposed to TCDD and TBrDD in 1956

Figure 12 illustrates an occupational hazard for dioxin chemists. A chemist was exposed to dioxins 34 and 35 years before blood samples were taken for analysis (13). He had first synthesized and then purified 2,3,7,8-tetrabromo-*p*-dioxin (2,3,7,8-TBrDD) and later 2,3,7,8-TCDD in 1956 at a university research laboratory. He developed chloracne, headaches, back-

aches, and severe pain in his legs when he walked. He was hospitalized primarily for medical evaluation and rapidly recovered, with only symptomatic treatment for his skin lesions. This incident was first described by Baughman in his 1974 Ph. D. thesis (1). In 1990 and again in 1991, approximately 35 years after exposure, blood dioxin analysis was performed to determine if a residual increase in dioxin levels existed. We found 20 ppt of TCDD and 625 ppt of TBrDD on a blood-lipid basis. This compares to the 3–5 ppt of TCDD usually measured in adults in the United States; 2,3,7,8-TBrDD has not been found in the general population despite measurements with a detection level in the low part per trillion range.

### U.S. Military Personnel Exposed to Agent Orange in Vietnam

Figure 13 summarizes our findings from another type of occupational exposure (34). In Vietnam, between 1962 and 1970, over 12 million gallons of Agent Orange, a phenoxyherbicide mixture of one-half butyl ester of 2,4 dichlorophenoxyacetic acid (2,4-D) and one-half butyl ester of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated with an average of 2–3 ppm 2,3,7,8-TCDD, was sprayed from fixed-wing aircraft by the U.S. Air Force to defoliate jungles and farmland. Over 12 million gallons were sprayed in this program, code named "Ranch Hand." Approximately 20 years after exposure, we measured 2,3,7,8-TCDD in the adipose tissue of six of these former sprayers. Levels from 17–55 ppt lipid of TCDD were found. Levels are estimated to have been from 140 to 610 ppt at time of

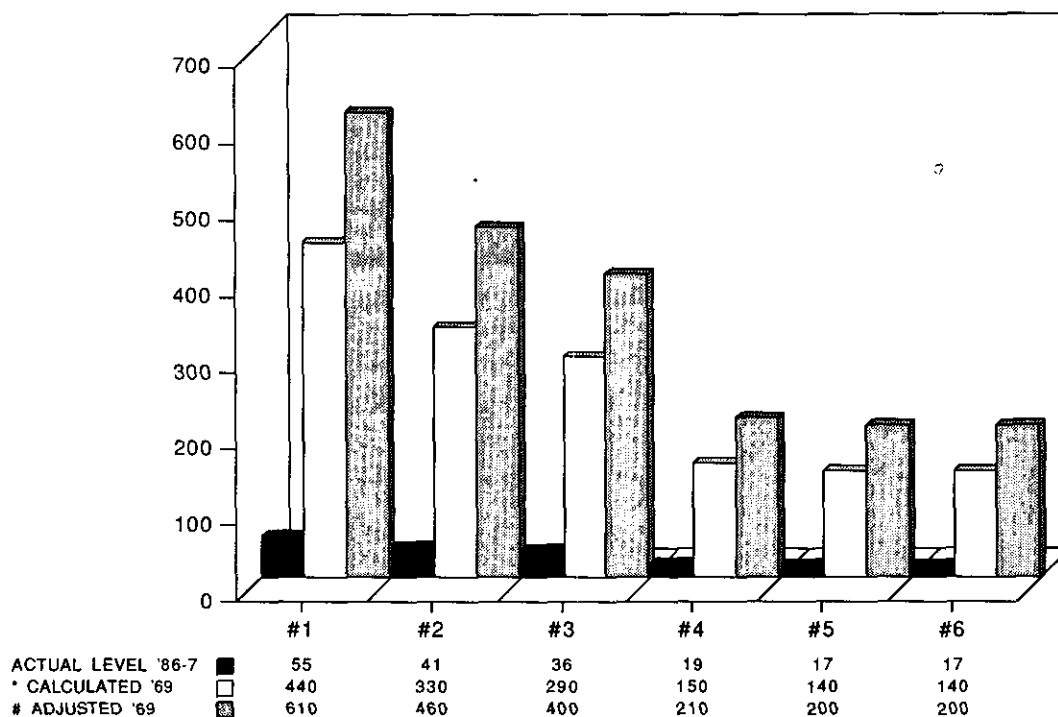


FIGURE 13. U.S. military personnel: 2,3,7,8-TCDD in adipose tissue (ppt, weight wet; lipid 97%) of veterans exposed to Agent Orange. (\*) Calculated using 3–6-year half-lives; (#) adjusted for 1.4 increase in body fat.

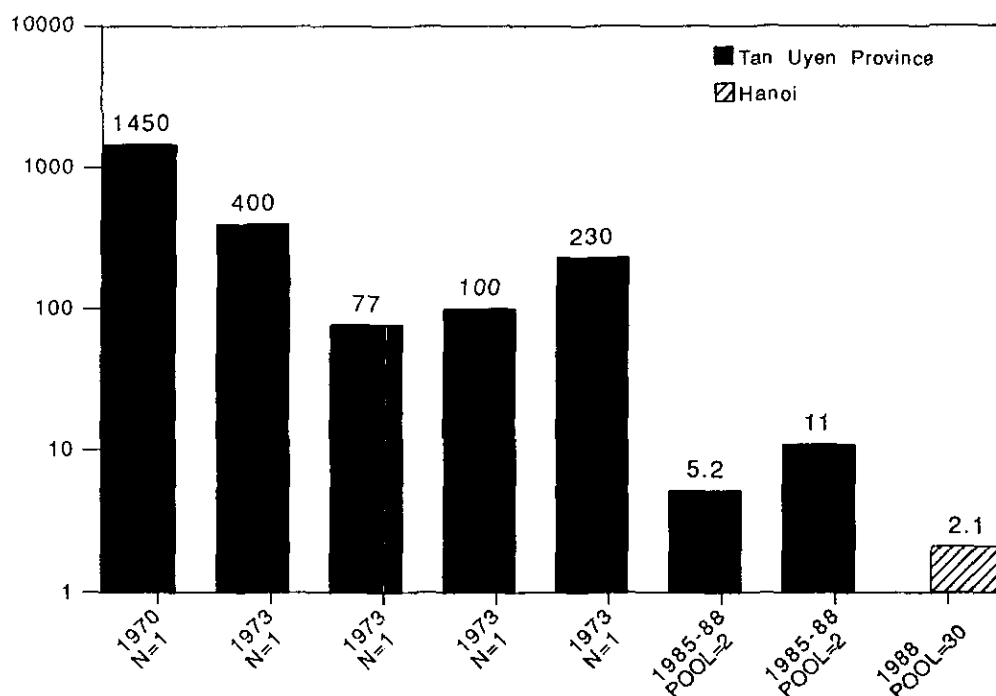


FIGURE 14. Vietnamese exposure to Agent Orange. 2,3,7,8-TCDD in human milk (ppt, lipid) from southern and northern Vietnam collected from 1970 to 1988. Tan Uyen Province is in southern Vietnam, Hanoi is in northern Vietnam.

exposure. Corrections were made for assumed half-life and also for assumed increased fat content with age in these workers, which is believed to dilute present levels.

## Vietnamese Exposed to TCDD from Agent Orange

Similar findings, but with sometimes higher levels of 2,3,7,8-TCDD, have been reported from the Vietnamese population who lived in areas sprayed with Agent Orange in the south of Vietnam (35-38). Breast milk 2,3,7,8-TCDD levels from residents of Tan Uyen Province are shown in Figure 14 (1,35). One sample measured in 1970 (the last year of spraying), had 1450 ppt lipid of TCDD, the highest dioxin level found in human breast milk to date. In 1973, levels from 77 to 400 ppt were found in human milk lipid from Vietnamese women nursing in these same villages. Between 1985 and 1990, we (35-38) collected and measured dioxins in milk from nursing mothers residing in sprayed areas in Vietnam and found much lower levels of TCDD. In the north of Vietnam, where no spraying occurred and where little industrial pollution existed, even lower levels of TCDD (as well as other dioxins from other sources) were found; here there was a TCDD level of 2.1 ppt lipid) from a pool of 30 nursing mothers living in Hanoi in 1984. The elevated TCDD findings document exposure to and actual intake of varying amounts of this dioxin from the same incident in both the workers who performed the spraying and the residents who lived in the sprayed area. In this instance, the same incident produced both an occupational and an environmental hazard. Lesser concentrations

of dioxin-contaminated phenoxyherbicides, such as 2,4,5-trichlorophenoxyacetic acid, were widely used in the United States and elsewhere. The more intense application of phenoxyherbicides in Vietnam may provide estimates of an upper exposure to and intake of TCDD from these herbicides in agricultural sprayers, and other military personnel, and also in the sprayed Vietnamese, who are the largest group potentially contaminated.

Agent Orange, characterized by 2,3,7,8-TCDD contamination, generated a great deal of interest in this dioxin congener. Figure 15 compares 2,3,7,8-TCDD levels to total dioxin and dibenzofuran TEQ levels in adipose tissue obtained in 1984 from Vietnamese hospitalized in the south of Vietnam in Ho Chi Minh City and from residents of the north of Vietnam in Hanoi (38). The Vietnamese population's exposure to Agent Orange was of lengthy duration due to their continued residence in the contaminated area, whereas the U.S. veterans served in the affected area for 1 year, or rarely for 2 years. Total PCDD/F TEQ levels in adipose tissue from Vietnamese living in Vietnam in the 1980s varied between 12 and 143 ppt in Ho Chi Minh City (formerly Saigon and surrounding areas) with TCDD ranging from not detected with a detection limit of 2 ppt to 103 ppt. In light of recent epidemiological findings linking phenoxyherbicides (in some cases not contaminated with TCDD) and 2,3,7,8-TCDD to cancer in humans (39-46), these findings may be of clinical concern.

In Figure 16, which depicts 2,3,7,8-TCDD and total PCDD/F TEQs in blood from Vietnam, geographical variation in dioxin levels can be observed. The northern samples have characteristically low levels, and in the south, long after Agent



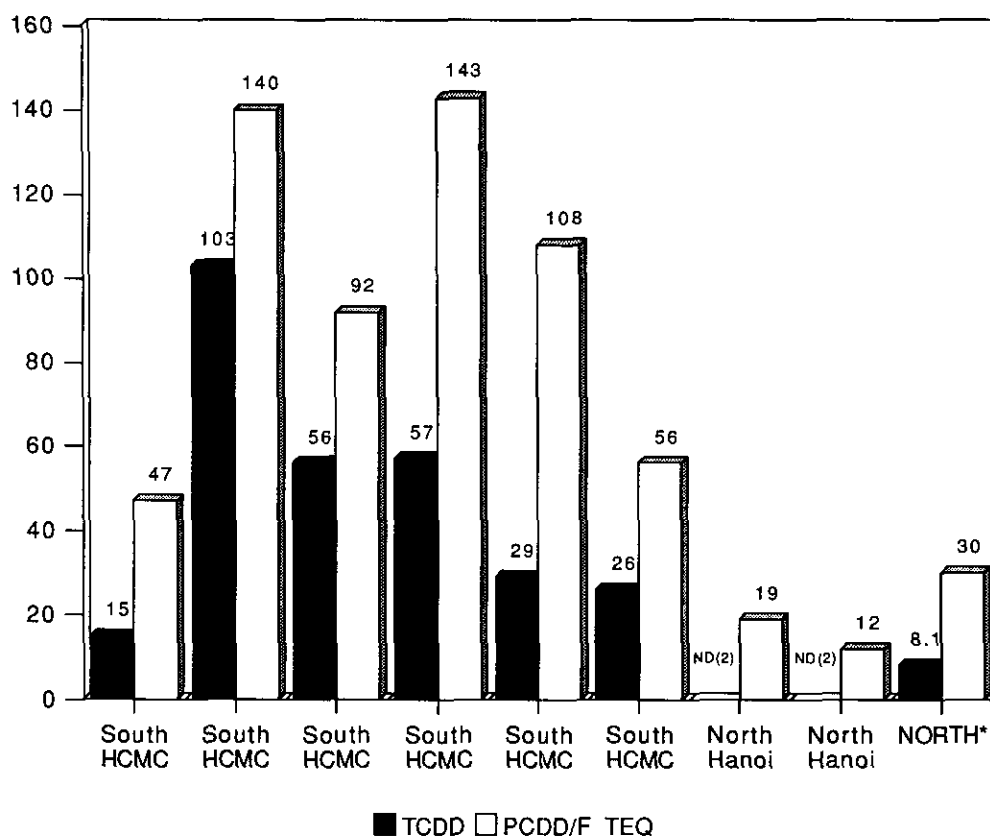


FIGURE 15. Vietnamese exposure to Agent Orange. TCDD and total TEQ in adipose tissue (ppt, lipid) comparing levels from the south to those from the north. (HCMC) Ho Chi Minh City. All are individual analyses except "North\*," which is a pool of 10 soldiers of the North Vietnamese Army who served in Agent Orange-sprayed areas in the south. Detection limit is 2 ppt.

Orange contamination, there are still populations with higher levels, with regional variations noted in central and southern Vietnam. These large populations with higher levels (in the south) and lower levels (in the north) present a unique opportunity for studying dioxin body burdens associated with disease states.

### Yusho Rice Oil Poisoning with PCDFs and PCBs, Japan, 1968

Figure 17 (47) illustrates dioxin and dibenzofuran congener levels from a well-known rice oil poisoning, the Yusho incident of 1968 in Fukuoka, Japan (48,49). In this incident, rice oil used for cooking was contaminated with PCBs, PCDFs, and PCDDs. About 2000 persons became sick and were treated by a special medical team. The illnesses were similar to those documented in animal studies with dioxins and with PCBs and from occupational exposures to dioxins and dioxin-like chemicals. It is believed that the toxic effects, based on amounts present and relative congener toxicity were primarily from the dibenzofurans, especially 2,3,7,8-substituted penta-, hexa- and hepta-

chlorinated congeners. PCBs are believed to have contributed to a lesser extent, and a small contribution to total toxicity is thought to have come from the dioxins and other chemicals. An adipose sample was taken from a victim 17 years after the 1968 incident to see if elevated levels could still be detected. Due to the very high dose, three of the dibenzofurans typical of the Yusho poisoning were still found to be elevated in this patients' adipose tissue. These are 2,3,4,7,8-PeCDF, total HxCDF, and 1,2,3,4,6,7,8-HpCDF. An almost identical incident occurred in Taiwan in 1979 with involvement of similar congeners (50,51). The Binghamton incident, as noted previously, showed elevation of some of these congeners in some exposed workers.

Figure 18 presents the Yusho data above for total PCDD, PCDF, and PCDD/F levels after conversion to TEQs. The PCDFs are seen to be markedly elevated (5386 versus 113 ppt for controls). Because of this, total PCDD/Fs are higher than in controls, 5764 as compared to 1648 ppt. PCDD toxic equivalents are identical in both, but PCDF TEQs are elevated, at 1363 ppt in this Yusho patient compared to 18 ppt in the controls. Thus, the total TEQ is still markedly higher (1387 ppt compared to 42 ppt in controls), even in the specimen obtained 17 years after exposure.

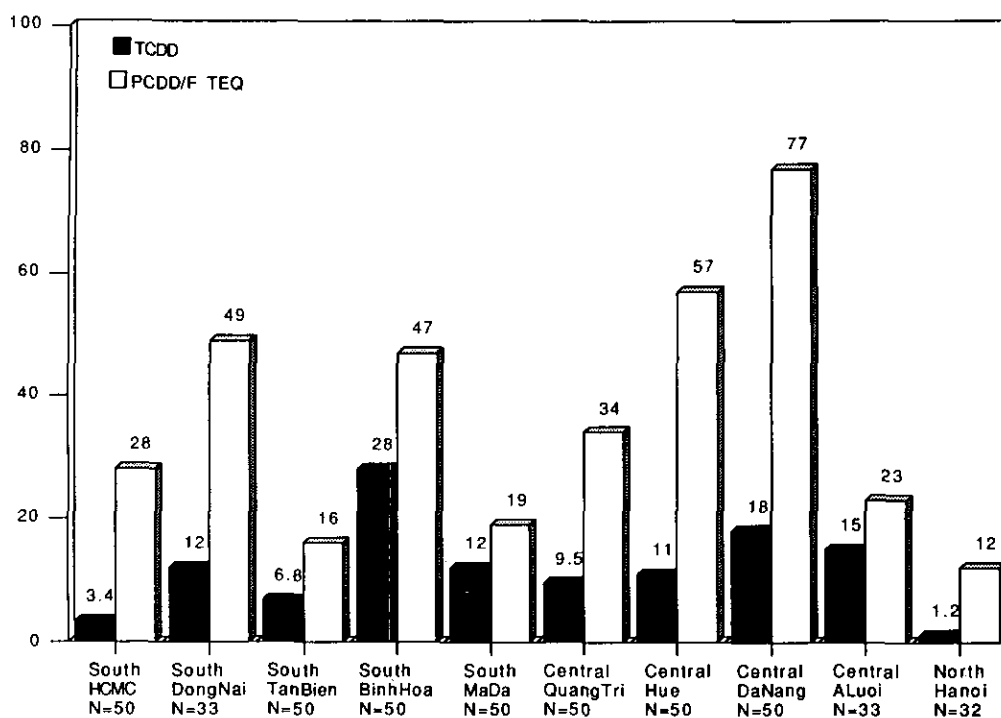


FIGURE 16. Vietnamese exposure to Agent Orange. TCDD and PCDD/F toxic equivalents in pooled blood (ppt, lipid) comparing levels from the south to those from the north. (HCMC) Ho Chi Minh City.

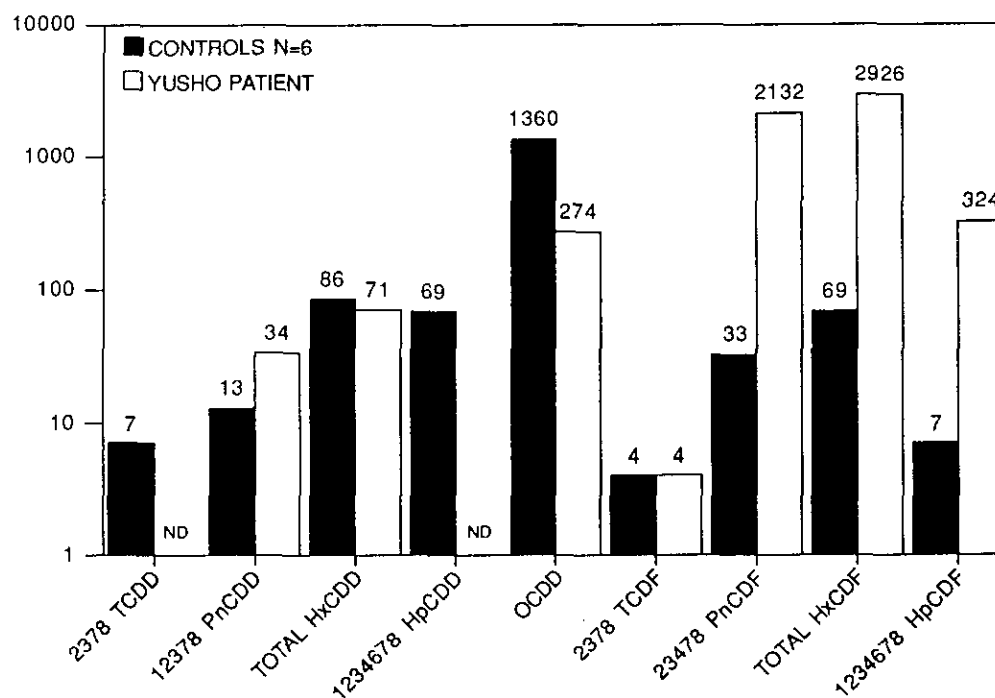


FIGURE 17. Yusho poisoning in Japan. PCDD/F congener levels in adipose tissue (ppt, lipid) from a patient 17 years after exposure compared to controls.

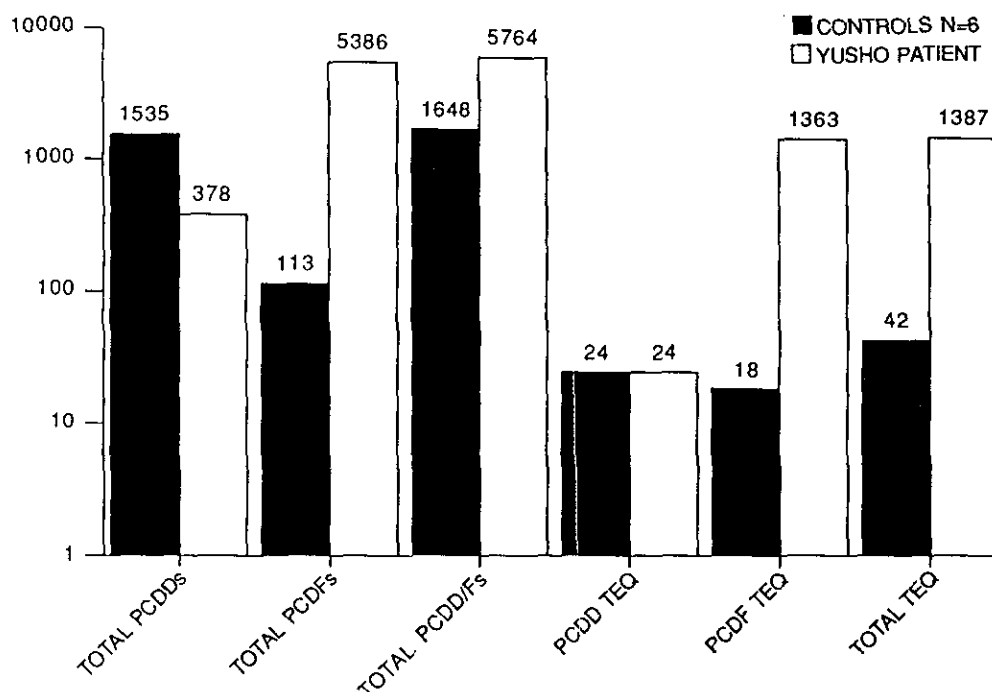


FIGURE 18. Yusho poisoning in Japan. PCDD/F and total (TEQ) levels in a Yusho patient and in controls (ppt, lipid).

## Conclusions

We have reviewed some relatively recent incidents of dioxin and dibenzofuran contamination where human tissue PCDD/F levels were determined to illustrate the use of such measurements in evaluation of exposed populations. Human tissue measurement for dioxins and dibenzofurans is relatively new and is just now beginning to be exploited in medicine and epidemiology. This is in part because the recent origin of most chlorinated dioxins and dibenzofurans. Also, the measurement of them in the environment and in humans is historically quite recent (52-57).

The serial determinations in a worker after exposure following a PCB transformer fire add to the evidence that some of the dibenzofuran congeners are eliminated in humans more rapidly than is the case for 2,3,7,8-TCDD. Thus, time after exposure is an important consideration in use and interpretation of dioxin tissue measurement. Also, relatively low levels, as seen in one of our Binghamton workers, may or may not have been higher than what existed before exposure, if the initial levels were below average general population values. Similar findings have been reported in published studies of "Ranch Hand" Agent Orange sprayers, where no detectable levels of TCDD were found in some subjects despite probable heavy exposure (58). Variation in absorption or excretion, laboratory error in analysis, or even mislabeling or mixing of specimens might be possible explanations for unexpectedly low values.

For the German workers and the dioxin chemist, detection of elevated chlorinated and brominated dioxins up to 35 years after exposure documents remarkable persistence for 2,3,7,8-substituted TCDD and TBrDD and points out potential long-term health hazards. The finding of elevated levels in these cases also

may be useful in workers' compensation hearings and as a way to estimate potential risk above background in populations or in individuals. The levels related to human health effects are not yet well characterized. There is recent evidence suggesting that humans may be at least as sensitive to certain dioxin-induced biochemical end points as are laboratory animals (59,60). Another case history illustrated dioxin contamination of American veterans and Vietnamese residents from herbicides contaminated with dioxins more than 20 years after the last application of Agent Orange in Vietnam.

There is also evidence that there may be neurodevelopmental and other adverse health outcomes in children exposed *in utero* and/or by nursing to the closely related dioxinlike compounds PCBs and PCDFs (61-65). It would seem prudent to consider adverse health outcomes such as neurological, immune deficiency, or reproductive outcomes, rather than focus exclusively on the better-characterized cancer-inducing capability of the dioxins and related chemicals.

Little work has been done so far to correlate fat and blood dioxin levels to target organ levels (66). Much work also remains to be done to characterize effects on blood dioxin levels during fasting and weight loss, during starvation, or during the wasting syndromes noted in diseases such as cancer, AIDS, and some other infectious diseases.

To date, these early studies on human tissue levels of dioxins and dibenzofurans appear to be promising with respect to their usefulness in medicine and medical research, but a great deal of work remains to integrate this valuable new technique into clinical medicine. Not the least of the problems is determining a routine method for funding the analyses when they are medically or scientifically indicated.

Some of the studies cited here have been made possible by the generous assistance of the Christopher Reynolds Foundation, the Samuel Rubin Foundation, the CS Fund, Church World Service, CIDSE, the Commonwealth of Massachusetts, and the American Association for the Advancement of Sciences and the National Academy of Sciences for the work done originally in Vietnam and on Vietnamese milk, food, and wildlife specimen from 1969 to 1974. The expert technical assistance in preparation of this manuscript is due to Ruth Stento and Karan Charles. Most of all, we extend our thanks to the patients involved.

## REFERENCES

- Baughman, R. W. Tetrachlorodibenzo-p-dioxins in the Environment: High Resolution Mass Spectrometry at the Picogram Level. Ph.D. Thesis, Harvard University, Cambridge, MA, 1974.
- Baughman, R. W., and Meselson, M. An analytical method for detecting TCDD (dioxin): levels of TCDD in samples from Vietnam. *Environ. Health Perspect.* 5: 27-35 (1973).
- Gross, M. L., Lay J. O., Jr., and Lyon, P. A. 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of Vietnam veterans. *Environ. Res.* 33: 261-268 (1984).
- Schecter, A., Tierman, T., Taylor, M. L., VanNess, G. F., Garrett, J. H., Wagel, D. J., and Gitlitz, G. The use of fat biopsies to estimate patient exposure to polychlorinated dibenzofurans, polychlorinated dibenzoparadioxins, biphenylenes, and polychlorinated biphenyl isomers after an electrical transformer fire in Binghamton, New York. Presented at American Chemical Society 186th National Meeting, Washington, DC, 1983.
- Schecter, A. J., Schaffner, F., Tiernan, T., et al. Biological markers after exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls and related chemicals. Part II: Ultrastructural characterization of human liver biopsies. In: *Chlorinated Dioxins and Dibenzofurans in the Total Environment*, Vol. 2 (L. Keith, C. Rappe, and G. Choudhary, Eds.), Ann Arbor Science, Butterworth Publ, Stoneham, MA, 1985, pp. 247-265.
- Schecter, A., and Tiernan, T. Occupational exposure to polychlorinated dioxins, polychlorinated furans, polychlorinated biphenyls and biphenylenes after an electrical panel and transformer accident in an office building in Binghamton, NY. *Environ. Health Perspect.* 60: 305-313 (1985).
- Schecter, A. J., Ryan, J. J., Lizotte, R., Wing, F. S., Miller, L., Gitlitz, G., and Bogdasarian, M. Chlorinated dibenzodioxins and dibenzofurans in human adipose tissue from exposed and control New York State patients. *Chemosphere* 14 (6/7): 933-937 (1985).
- Ryan, J. J., Lizotte, R., and Lau, B. P. Y. Chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans in Canadian human adipose tissue. *Chemosphere* 14: 697-706 (1985).
- Schecter, A. J., Ryan, J. J., and Gitlitz, G. Chlorinated dioxin and dibenzofuran levels in human adipose tissues from exposed and control populations. In: *Chlorinated Dioxins and Dibenzofurans in Perspective* (C. Rappe, G. Choudhary, and L. Keith, Eds.), Lewis Publishers, Chelsea, MI, 1986, pp. 51-65.
- Päpke, O., Ball, M., Liz, Z. A., and Scheunert, K. PCDD/PCDF in whole blood samples of unexposed persons. *Chemosphere* 19: 941-948 (1989).
- Schecter, A., Ryan, J. J., Constable, J. D., Baughman, R., Bangert, J., Fürst, P., Wilmers, K., and Oates, R. P. Partitioning of 2,3,7,8-chlorinated dibenzo-p-dioxins and dibenzofurans between adipose tissue and plasma lipid of 20 Massachusetts Vietnam veterans. *Chemosphere* 20: 951-958 (1990).
- Schecter, A., and Ryan, J. J. Blood and adipose tissue levels of PCDDs/PCDFs over three years in a patient after exposure to polychlorinated dioxins and dibenzofurans. *Chemosphere* 18: 635-642 (1989).
- Schecter, A., and Ryan, J. J. Brominated and chlorinated dioxin blood levels in a chemist 34 years after exposure to 2,3,7,8-tetrachlorodibenzodioxin and 2,3,7,8-tetrabromodibenzodioxin. *Chemosphere* 23: 1921-1924 (1991).
- Schecter, A., Constable, J. D., Arghestani, S., Tong, H., and Gross, M. L. Elevated levels of 2,3,7,8-tetrachlorodibenzodioxin in adipose tissue of certain U.S. veterans of the Vietnam War. *Chemosphere* 16 (8/9): 1997-2002 (1987).
- Schecter, A., Haughe, G., and Rothenberg, R. PCB Transformer Fire—Binghamton, New York. *Morbidity Mortality Weekly Rep.* 30(16): 187-193 (1981).
- Schecter, A. J. Contamination of an office building in Binghamton, New York by PCB's, dioxins, furans and biphenylenes after an electrical panel and electrical transformer incident. *Chemosphere* 12(4/5): 669-680 (1983).
- Buser, H. Formation, occurrence and analysis of polychlorinated dibenzofurans, dioxin and related compounds. *Environ. Health Perspect.* 60: 259-267 (1985).
- Schecter, A. The Binghamton State Office Building PCB, dioxin and dibenzofuran electrical transformer incident: 1981-1986. *Chemosphere* 15(9/12): 1273-1280 (1986).
- Eadon, G., Kaminsky, L., Silkworth, J., Aldous, K., Hilker, D., O'Keefe, P., Smith, R., Gierthy, J., Hawley, J., Kim, N., and Decaprio, A. Calculation of 2,3,7,8-TCDD equivalent concentrations of complex environmental contaminant mixtures. *Environ. Health Perspect.* 70: 221-227 (1986).
- NATO. Pilot Study on International Information Exchange on Dioxins and Related Compounds. Scientific Basis for the Development of the International Toxicity Equivalency Factor (I-TEF): Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds. No. 176. North Atlantic Treaty Organization, Committee on the Challenges of Modern Society, 1988.
- NATO. Pilot Study on International Information Exchange on Dioxins and Related Compounds. Scientific Basis for the Development of the International Toxicity Equivalency Factor (I-TEF): Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds. No. 178. North Atlantic Treaty Organization, Committee on the Challenges of Modern Society, 1988.
- Beck, H., Eckart, K., Mathar, W., and Wittkowski, R. Levels of PCDD and PCDFs in adipose tissue of occupationally exposed persons. *Chemosphere* 18: 507-516 (1989).
- Mocarelli, P., Patterson, D. G., Marocchi, A., and Needham, L. Pilot study (phase II) for determining polychlorinated dibenzo-p-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) levels in serum of Seveso, Italy residents collected at the time of exposure: future plans. *Chemosphere* 20: 967-974 (1990).
- Ryan, J. J., Gasiewicz, T. A., and Brown, J. F., Jr. Human body burden of polychlorinated dibenzofurans associated with toxicity based on the Yusho and Yucheng incidents. *Fundam. Appl. Toxicol.* 15: 722-731 (1990).
- Schecter, A., Ryan, J. J., and Kostyniak, P. J. Decrease over a six year period of dioxin and dibenzofuran tissue levels in a single patient following exposure. *Chemosphere* 20(7/9): 911-917 (1990).
- Pirkle, J. L., Wolfe, W. H., Patterson, D. G., Needham, L. L., Michalek, J. E., Miner, J. C., Peterson, M. R., and Phillips, D. L. Estimates of the half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Vietnam veterans of Operation Ranch Hand. *J. Toxicol. Environ. Health* 27: 165-171 (1989).
- Schlatter, C., and Poiger, H. The need for kinetic considerations in the establishment of TEF-values. In: *Organohalogen Compounds*, Vol. 1. Ecoinforma Press, Bayreuth, Germany, 1990, pp. 333-340.
- Van den Berg, M., and Poiger, H. Toxicokinetic limitations in the present toxic equivalency (TEQ) concept. In: *Organohalogen Compounds*, Vol. 1 (O. Hutzinger and E. H. Fiedler, Eds.), Ecoinforma Press, Bayreuth, Germany, 1990, pp. 337-340.
- Gorski, T., Konopka, L., and Brodzki, M. Persistence of some polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans of pentachlorophenol in human adipose tissue. *Rocz. Panstw. Zakl. Hig.* 35: 297-301 (1984).
- Ryan, J. J., and Masuda, Y. Elimination of polychlorinated dibenzofurans (PCDFs) in humans from the Yusho and Yucheng rice oil poisonings. Presented at Dioxin '91, Research Triangle Park, NC. September 26, 1991.
- Schecter, A. J., and Ryan, J. J. Polychlorinated dibenzo-para-dioxin and dibenzofuran levels in human adipose tissues from workers 32 years after occupational exposure to 2,3,7,8-TCDD. *Chemosphere* 17(5): 915-920 (1988).
- Liem, A. K. D., Hoogerbrugge, R., Kootstra, P. R., van der Velde, E. G., and de Jong A. P. J. M. Occurrence of dioxins in cow's milk in the vicinity of municipal waste incinerators and a metal reclamation plant in the Netherlands. *Chemosphere* 23 (11/12): 1675-1684 (1991).
- Schecter, A. J., Malkin, R., Päpke, O., Ball, M., and Brandt-Rauf, P. W. Dioxin levels in blood of municipal incinerator workers. *Med. Sci. Res.* 19: 331-332 (1991).
- Schecter, A., Constable, J. D., Bangert, J. V., Tong, H., Arghestani, S., Monson, S., and Gross, M. Elevated body burdens of 2,3,7,8-tetrachlorodibenzodioxin in adipose tissue of United States Vietnam veterans. *Chemosphere* 18: 431-438 (1989).
- Schecter, A., Ryan, J. J., and Constable, J. D. Chlorinated dibenzo-p-dioxin and dibenzofurans levels in human adipose tissue and milk samples from the north and south of Vietnam. *Chemosphere* 15(9/12): 1613-1620 (1986).
- Schecter, A., Ryan, J. J., and Constable, J. D. Polychlorinated dibenzo-p-dioxin and polychlorinated dibenzofuran levels in human breast milk from Vietnam compared with cow's milk and human breast milk from the North American continent. *Chemosphere* 16(8/9): 2003-2016 (1987).

37. Schecter, A. J., Ryan, J. J., Gross, M., Weerasinghe, N. C. A., and Constable, J. Chlorinated dioxins and dibenzofurans in human tissues from Vietnam, 1983-1984. In: *Chlorinated Dioxins and Dibenzofurans in Perspective* (C. Rappe, G. Choudhary, and L. Keith, Eds.), Lewis Publishers, Chelsea, MI, 1986, pp. 35-50.
38. Schecter, A. J., Ryan, J. J., and Constable, J. D. Chlorinated dibenzo-p-dioxin and dibenzofuran levels in human adipose tissue and milk samples from the north and south of Vietnam. *Chemosphere* 15(9/12): 1613-1620 (1986).
39. Hoar, S. K., Blair, A., Holmes, F. F., Boysen, C. D., Robel, R. J., Hoover, R., and Fraumeni, J. F. Jr. Agriculture herbicide use and risk of lymphoma and soft-tissue sarcoma. *J. Am. Med. Assoc.* 156: 1141-1147 (1986).
40. Hardell, L., and Eriksson, M. Soft-tissue sarcoma and exposure to dioxins. *Lancet* 2: 1-868 (1986).
41. Hardell, L., and Eriksson, M. The association between soft tissue sarcomas and exposure to phenoxyacetic acids. *Cancer* 62: 652-656 (1988).
42. Hoar Zahm, S., Weisenburger, D. D., Babbitt, P. A., Saal, R. C., Vaught, J. B., Cantor, K. P., and Blair, A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1: 349-356 (1990).
43. Zober, A., Messerer, P., and Huber, P. Thirty-four year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 incident. *Int. Arch. Occup. Environ. Health* 62: 139-157 (1990).
44. Fingerhut, M. A., Halperin, W. E., Marlow, D. A., Piacitelli, L. A., Honchar, P. A., Sweeney, M. H., Griefe, A. L., Dill, P. A., Steenland, K., and Suruda, A. J. Cancer mortality in workers 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N. Engl. J. Med.* 324: 212-218 (1991).
45. Manz, A., Berger, J., Dwyer, J. H., Flesch-Janys, D., Nagel, S., and Waltsgott, H. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 338: 959-964 (1991).
46. Saracci, R., Kogevinas, M., Bertazzi, P. A., Mesquita, B. H. B. D., Coggon, D., Green, L. M., Kauppinen, T., L'Abbe, K. A., Littorin, M., Lynge, E., Matthews, J. D., Neuberger, M., Osman, J., P. Pearce, N., and Winkelmann, R. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 338: 1027-1032 (1991).
47. Ryan, J. J., Schecter, A., Masuda, Y., and Kikuchi, M. Comparison of PCDDs and PCDFs in the tissues of Yusho patients with those from the general population in Japan and China. *Chemosphere* 16(8/9):2017-2025 (1987).
48. Higuchi, K., Hirayama, C., Kikuchi, M., Koda, H., Kuratsune, M., Masuda, Y., Tanabe, H., Tatsukanwa, R., Veda, K., Vrahe, H., Yoshihara, S., and Yoshimura, H. *PCB Poisoning and Pollution*. Kodansh Ltd. Academic Press, Tokyo 1976.
49. Kasimoto, T., Miyata, H., Kunita, S., Tung, T., Hsu, S. T., Chang, K. J., Tang, S. Y., Ohi, G., Nakagawa, J., and Yamamoto, S. I. Role of polychlorinated dibenzofuran in Yusho (PCB poisoning). *Arch. Environ. Health* 36: 321 (1981).
50. Kashimoto, T., Miyata, H., Fukushima, H., and Kunita, N. Study on PCBs, PCDFs in the blood of Taiwanese patients with PCB poisoning and the casual cooking of rice bran oil. *Fukuoka Acta Med.* 74: 255 (1983).
51. Kuratsune, M., and Shapiro, R., Eds. *PCB Poisoning in Japan and Taiwan*. Alan R. Liss, New York, 1984.
52. Czuczwa, J. M., and Hites, R. A. Sources and fate of PCDD and PCDF. *Chemosphere* 15: 1417-1420 (1986).
53. Czuczwa, J. M., McVeety, B. D., and Hites, R. A. Polychlorinated dibenzo-p-dioxins and dibenzofurans in sediments from Siskiwit Lake, Isle Royale. *Science* 226: 568-569 (1984).
54. Schecter, A. J., Eitzer, B. D., and Hites, R. A. Chlorinated dioxin and dibenzofuran levels in sediments collected from rivers in Vietnam, 1984-6. *Chemosphere* 18: 831-834 (1989).
55. Schecter, A. J., Tong, H. Y., Monson, S. J. and Gross, M. L. Levels of 2,3,7,8-TCDD in silt samples collected between 1985-86 from rivers in the north and south of Vietnam. *Chemosphere* 19: 547-550 (1989).
56. Schecter, A., Dekin, A., Weerasinghe, N. C. A., Arghestani, S., and Gross, M. L. Sources of dioxins in the environment: a study of PCDDs and PCDFs in ancient, frozen Eskimo tissue. *Chemosphere* 17(4): 627-631 (1987).
57. Tong, H. Y., Gross, M. L., Schecter, A., Monson, S. J., and Dekin, A. Sources of dioxins in the environment: second stage study of PCDD/Fs in ancient human tissue and environmental samples. *Chemosphere* 20(7/9): 987-992 (1990).
58. Lathrop, G. D., Wolfe, W. H., and Albanese, R. A. Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. Serum Dioxin Analysis. Epidemiology Research Division, Armstrong Laboratory Human Systems Division, Brooks Air Force Base, TX, 1991.
59. Lucier, G. W. Humans are a sensitive species to some of the biochemical effects of structural analogs of dioxin. *Environ. Toxicol. Chem.* 10: 727-735 (1991).
60. Lucier, G. W., Nelson, K. G., Everson, R. B., Wong, T. K., Philpot, R. M., Tiernan, T., Taylor, M. and Sunahara, G. I. Placental markers of human exposure to polychlorinated biphenyls and polychlorinated dibenzofurans. *Environ. Health Perspect.* 76: 79-87 (1987).
61. Gladen, B. C., Taylor, J. S., Wu, Y. C., Ragan, N. B., Rogan, W. J., and Hsu, C. C., Dermatological findings in children exposed transplacentally to heat-degraded polychlorinated biphenyls in Taiwan. *B. J. Dermatol.* 122: 799-808 (1990).
62. Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tinglestad, J., and Tully, M. Neonatal effects of transplacental exposure to PCBs and DDE. *J. Pediatr.* 109: 335-341 (1986).
63. Fein, G. G., Jacobson, J. L., Jacobson, S. W., Schwartz, P. M., and Dowler, M. A. Prenatal exposure to polychlorinated biphenyls: effects on birth size and gestational age. *J. Pediatr.* 105: 315-320 (1984).
64. Jacobson, S. W., Jacobson, J. L., Schwartz, P. M., and Fein, G. G. In-uterine exposure of human newborns to PCBs. In: *Human and Environmental Hazards* (F. M. D'Itri and M. Kamrin, Eds.), Butterworth, Boston, 1983, pp. 311-343.
65. Jacobson, J. L., Fein, G. G., Jacobson, S. W., Schwartz, P. M., and Dowler, J. K. The transfer of polychlorinated biphenyls and polybrominated biphenyls across the human placenta and into the maternal milk. *Am. J. Public Health* 74: 378-379 (1984).
66. Ryan, J. J., Schecter, A., Lizotte, R., Sun, W. F., and Miller, L. Tissue distribution of dioxins and furans in humans from the general population. *Chemosphere* 14(6/7): 929 (1985).